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Predisposition to breast cancer is inherited as a genetic trait in some families. Thus far, a few highly penetrant genes responsible for inherited breast cancer have been identified. An important and unresolved question of breast cancer etiology is whether there are other genes which have a more moderate effect on breast cancer risk, possibly triggering disease only in the presence of specific environmental exposures, and possibly involving more women than do other, highly penetrant mutations. It has been suggested that mutations in the Ataxia-Telangiectasia gene (ATM) and radiation exposure could be involved with breast cancer in this manner. In order to address this question, we are screening a series of breast cancer patients for mutations in the ATM gene. This series of patients was selected for either radiation exposure, radiation sensitivity, inheritance of a single ATM allele through multiple affected members of a family, or having a child with Ataxia-Telangiectasia. This study will detect potential mutations in the ATM gene which confer breast cancer risk, particularly mutations which may lead to radiation sensitivity.

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Elizabeth Schubert 8/28/97

PI - Signature Date

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Elizabeth L. Schubert, Ph.D.
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Introduction

Predisposition to breast cancer is inherited in an autosomal dominant manner in some individuals (Newman et al 1988). Currently, the inheritance of breast cancer predisposition is clearly associated with a few highly penetrant genes, such as BRCA1, in rare families (reviewed in Szabo and King 1995). A crucial and still unresolved question in inherited predisposition to breast cancer is whether germline alterations in other, yet-undefined genes could confer a moderately increased risk of breast cancer, potentially with disease expression among mutation carriers dependent on specific environmental exposures. Such low penetrance genetic predisposition could account for a greater population risk of breast cancer than the relatively rare highly penetrant gene mutations, although it would convey less risk to individual heterozygotes. One gene that has been suggested to play a role in moderately increased risk of breast cancer is the gene mutated in Ataxia-Telangiectasia (ATM). This study seeks to clarify the role of ATM in breast cancer predisposition. Specifically, this study asks whether ATM heterozygotes are predisposed to breast cancer, particularly when they are exposed to environmental radiation.

Ataxia-Telangiectasia (AT) is a recessive genetic disorder (reviewed in Lavin and Shiloh, 1997) characterized by progressive cerebellar ataxia, blood vessel lesions (telangiectasias) and immunodeficencies. Patients affected with AT are prone to develop lymphoma and leukemia and are extremely sensitive to ionizing radiation. Various regions of ATM have been identified as specific functional domains, including a carboxy-terminal protein kinase domain (Savitsky et al 1995a, Savitsky et al 1995b). The ATM gene product has been shown to play an important role in cellular response to DNA damage, particularly that from ionizing radiation, as a component of a cell-cycle checkpoint pathway (reviewed in Hoekstra 1997). All AT patients identified to date have inherited two germ-line mutations at the ATM locus. Multiple mutations in ATM have been discovered in AT patients worldwide (The Ataxia-Telangiectasia Mutation Database), with some founder effects of particular mutations in defined populations (Chessa et al 1997, Gilad et al 1996). Most ATM mutations identified to date are protein truncating alterations in AT patients with the classically identified severe disease phenotype, however some studies have found evidence of particular ATM mutations which are associated with variant phenotypes (Bar-Shira et al 1997, Taylor et al 1997, McConville et al 1996).

Epidemiological studies of the families of children suffering from AT have shown an increased incidence of cancer, particularly breast cancer, in the relatives of such patients (Athma et al 1996, Easton 1994, Pippard et al 1988, Swift et al 1987). Family studies have also suggested that exposure to ionizing radiation increases cancer risk in ATM heterozygotes (Swift et al 1991), which is a compelling idea, particularly given the sensitivity of AT patients to radiation and the known function of the ATM gene product in cellular response to DNA damage. The focus of our study has been to investigate this question by examining breast cancer patients, particularly those who have been exposed to ionizing radiation or who show an extreme response to such radiation, for ATM heterozygosity. Such a breast cancer patient-based approach complements the studies of AT families which have already been reported.

Body of Report

Experimental Methods, Assumptions and Procedures

This study is based on the hypothesis that ATM heterozygotes have an increased susceptibility to breast cancer, particularly when exposed to ionizing radiation. We originally proposed to screen a large, population-based series of breast cancer patients for alterations in the ATM gene. However, more recent reports that ATM heterozygosity is not found in a large number of breast cancer patients (FitzGerald et al 1997, Vorechovsky et al 1996a, Vorechovsky et al 1996b) has caused us to redirect our efforts to a more focused group of patients than was originally proposed. One previous study (FitzGerald et al 1997) examined 401 women diagnosed with breast cancer under the age of 40 for mutations in ATM. Two of the 401 women (0.5%) had detectable mutations in ATM, a fraction not significantly different than that found in the general population, leading the investigators to conclude that ATM heterozygosity was not prevalent in early-onset breast cancer patients. However, if ATM heterozygotes are increasingly predisposed to breast cancer after exposure to radiation, possibly with a lengthy time interval in which cancer is forming but undetectable by routine clinical means, these findings in young, mainly unexposed patients are not surprising. In the series of 401 patients, only 11 had been previously exposed to radiation (2.7%). An additional phenotype which may be associated with ATM heterozygote breast cancer patients is sensitivity to radiation treatment, a condition which would mimic but be less severe than the radiation sensitivity of AT patients themselves. Such a phenotype would be consistent with *in vitro* observations that cells from ATM heterozygotes exhibit an intermediate level of radiation sensitivity between that of wild type individuals and AT patients (West et al 1995, Thacker 1994). Of the series of 401 patients reported by FitzGerald et al, only 2 were reported as radiation sensitive out of the 207 women who had undergone radiation therapy for breast cancer (<1%). In the studies by Vorechovsky et al, 88 breast cancer patients from families with other cancer incidence and 38 serially-ascertained breast tumors were screened for mutations in ATM. In the individual probands, 3 mutations in ATM and 8 polymorphisms were detected, while in the tumor samples 5 polymorphisms were detected. No clinical data was given by Vorechovsky et al on the radiation exposure or radiation sensitivity of the patients who donated samples to their study, however the average age of diagnosis was 53 years for the breast cancer probands and 55.8 years for the tumor samples, considerably older than the patients in the FitzGerald series. What these three studies, taken together, indicate is that a general screen of breast cancer patients, including those with early-onset disease, is unlikely to uncover ATM mutations. However, these previous studies do not take into account the possibility of an increased susceptibility to breast cancer in ATM heterozygotes over time after radiation exposure and the possibility of ATM heterozygotes exhibiting a phenotype of radiation sensitivity during breast cancer treatment.

Although most of the ATM mutations identified to date lead to protein truncation (Gilad et al 1996, The Ataxia-Telangiectasia Mutation Database), some studies have identified particular mutations which lead to distinct sub-phenotypes (Bar-Shira et al 1997, Taylor et al 1997, McConville et al 1996). It is possible that particular mutations in ATM lead to a greater susceptibility to breast cancer due to their particular effects on the ATM protein. Preliminary data from British AT families suggests such a mutation in that population (Taylor et al 1997). The FitzGerald and Vorechovsky studies have also found ATM mutations in samples from breast cancer patients, although they did not expand their populations on discuss the clinical details of the patients with mutations. The British mutation is particularly interesting as the increased risk of cancer is associated with a less severe AT phenotype, possibly due to the particular functional domain of the gene which is affected. More studies are required to examine the possible existence of particular ATM mutations that increase susceptiblity to breast cancer in heterozygotes and their prevalence worldwide.

Given the information outlined above, which was not available at the time of writing our original proposal, we have changed the focus of our ATM screening in breast cancer patients. The population of patients that we are now screening for ATM mutations reflects a redefinition of our original hypothesis, which is that ATM heterozygotes with breast cancer may show either a

particular phenotype or have particular mutations which predispose them to cancer. We are pursuing this hypothesis by screening patients which, based on the information available to date, have phenotypes that are most likely to be associated with ATM mutations. Our current series of breast cancer patients being screened for ATM mutations are taken from the following groups: previous radiation exposure, radiation sensitivity, families with at least 3 cancer cases and the common inheritance of a single ATM allele between affected members, or a breast cancer patient who has had a child with AT. Given the relative rarity of each of these phenotypes, the current series of patients is smaller than that originally proposed, however given current understanding of ATM, we feel that this series has greater potential to uncover a link between ATM mutations and breast cancer predisposition. We began this genetic screening with regions of ATM in which the most common previously seen mutations occur, including those which have been previously reported in breast cancer patients. Any positive results from this study, either in patients with a particular phenotype or a unique mutation, will be the preliminary data needed to expand the screening series to more patients from an appropriate group.

The specific patients currently being screened for mutations in ATM are: 8 breast cancer patients who exhibited a severe sensitivity to radiation therapy for their cancer, 5 families with at least 3 cancer cases and the common inheritance of a single ATM allele between affected family members, 2 patients who had received radiation therapy for Hodgkin's Lymphoma before being diagnosed with breast cancer, and one set of parents of an AT child. The 5 families included in this study include 3 families with 3 cases of breast cancer, one family with 2 cases of breast and 2 cases of ovarian cancer, and one family with 1 breast, 2 ovarian, 2 colon and 5 prostate cancer cases. This range of cancer types is consistent with those seen in AT families (Morrell et al 1990). Previous BRCA1 and BRCA2 mutation testing in these families was negative. The mother of the AT child reports that she stood next to her son during his radiation therapy for cancer and that her breast subsequently affected with cancer was within the field of this radiation exposure. Her husband was included in this series as a positive control for ATM mutation detection, as the father of an AT child he is an obligate heterozygote. In the aggregate, we believe that screening this series of patients will indicate which phenotype is associated with ATM mutations and if there is evidence for particular ATM allele(s) which cause a particular susceptibility to breast cancer. The series of radiation sensitive breast cancer patients is particularly interesting, given previous data regarding the radiation sensitivity of cells taken from AT heterozygote patients (West et al 1995, Thacker 1994) and the role of ATM in cellular response to radiation (reviewed in Hoekstra 1997). All patients were enrolled in the study after appropriate informed consent within the structure of our University of Washington Institutional Review Board for Human Subjects agreement.

Since the original submission of this grant, the complete cDNA sequence, genomic organization, and genomic sequence of ATM have been published (Savitsky et al 1995b, Uziel et al 1996, Platzer et al 1997), eliminating the need to obtain this information from other sources. Our preliminary screening strategy for this set of patients has been targeted screening by single-strand conformational analysis (SSCA) of genomic DNA for ATM mutations with known genomic causes reported multiple times (Table 1). Many of the mutations identified in ATM to date are deletions in cDNA for which the genomic basis is unclear, such variants were disregarded in this targeted screen as they have the potential to be artifacts. The polymerase chain reaction (PCR) primers used in this SSCA analysis were those of Vorechovsky et al (1996a). Fragments screened to date include 2562 nucleotides of the 9168 nucleotides of the ATM coding region (Savitsky et al 1995b). This encompasses nearly 30% of the ATM coding region and the adjoining mRNA splicing regions of the exons examined. Results from the initial screen are described below. The next phase of this project will be to screen the entire ATM coding region in cDNA made from lymphoblastoid samples from patients in this series.

Results and Discussion

To date, we have screened all samples by SSCA through all the fragments listed in Table 1. One variant has been detected in 3 of the 8 radiation sensitive breast cancer patients and one variant has been detected in a single individual from each of 2 cancer families. Since the variants detected

in the families do not segregate with the commonly inherited ATM allele, they are likely to be polymorphisms. Sequencing of all variants is currently underway.

The next stage of the screen will be to examine cDNA made from lymphoblasts to detect potential variants in ATM. We currently have in the laboratory the RNA sources needed to make cDNA from all members of the screening series. The technique that we will use to screen these cDNAs for variants is restriction endonuclease fingerprinting (REF; Liu and Sommer 1995), a method which has been used previously on the ATM gene with success (Gilad et al 1996). We will use the same protocol as Gilad et al, which is a combination of common techniques already present in the lab, such as cDNA synthesis, restriction enzyme digestion and PCR.

Future plans are to expand this preliminary patient series as warranted from initial results. If there is evidence for ATM mutations in a particular group of breast cancer patients (such as the radiation sensitive patients) or for particular ATM mutation(s) present in breast cancer patients, then we will expand the study to include more patients from the relevant group. For example, if we find evidence for ATM mutations in the radiation sensitive breast cancer patients, we will expand our ATM screening to more such patients. At this time we have available samples from only the 8 radiation sensitive patients currently in our series, however with positive preliminary data on ATM mutations we would be able to embark on collaborations with our clinical colleagues to obtain more such patient samples. Alternatively, if there is evidence for a particular ATM mutation which predisposes to breast cancer, we will expand our screen for that ATM mutation in more breast cancer patients. Functional analysis of any ATM mutation would also be carried out, as discussed in the original proposal. LOH at the ATM locus in tumors from patients with ATM mutations is also planned, as discussed in the original proposal. We have already obtained tumor samples from the families involved in this study, other samples will be available as needed. Family cancer histories will be taken from any individual probands with ATM mutations and relevant family members will be asked to participate in the study.

Recommendations Relating to Statement of Work (SoW)

Month 1: Develop SSCA primers for ATM gene screening

SSCA primers for the ATM gene have been developed, and the additional technique of REF has been added to the mutation screening approach. The REF technique will be proceeding in the immediate future; there is a defined REF protocol for ATM and we already have expertise in the component parts of the protocol.

Months 1-30: Analyze CBCS DNA samples for mutations at the ATM locus

The original SoW called for mutation analysis of patient samples to be completed in the first 30 months of this grant; we will continue with that target date.

Months 12-30: Analyze tumor samples for LOH at the ATM locus

Tumor samples from patients with ATM mutations will be examined for LOH within the original time frame proposed. Already available in the laboratory are samples from the families enrolled in our screening set, other tumor samples will be obtained as necessary.

Months 12-35: Carry out functional analysis of ATM mutations identified

Functional analysis of the ATM mutations identified will be carried out in the original time frame proposed.

Months 2-31: Examine family history of individuals found to carry ATM mutations

Any individual probands found to have an ATM mutation will be examined for their family history of cancer and any relevant family members will be asked to participate in this study, an expansion from the original goals. Some families are being included in the current screening set as a unit, in these cases the family history of cancer is already well defined.

Months 30-36: Perform statistical analysis of data collected

As the samples being screened for ATM mutations are no longer a population-based series, the appropriate statistical analysis has changed. Penetrance of ATM mutations can, however, be calculated based on an analysis of family history and testing individual family members for their mutation status (Schubert et al 1997a).

Conclusions

This work is currently too preliminary for any conclusions to be drawn about the relevance of ATM mutations to inherited predisposition to breast cancer. Published studies on ATM mutations in breast cancer patients have caused us to rethink our approach to this problem but have not conclusively answered whether ATM mutations predispose heterozygous carriers to breast cancer.

Other studies: BRCA2 analysis

In December of 1995, while the proposal for this grant was under review, the BRCA2 gene was cloned, allowing us to screen individuals from high-risk cancer families for specific mutations in this gene and to use the data generated in such analysis to calculate risk estimates for disease in mutation carriers. Analysis of mutations in BRCA2 led to a better understanding of inherited predisposition to breast cancer directly attributable to that gene, information which is relevant to the study of predisposition to breast cancer as a whole. In a large sense, therefore, analysis of BRCA2 mutations falls into the scope of this grant subject. The cloning of BRCA2 also has direct relevance to the work described in this proposal as mutations in either BRCA2 or ATM are rare, and a person with predisposition to breast cancer arising from an inherited mutation in BRCA2 would be unlikely to also have an ATM mutation. Superficially, however, an individual with a mutation in either the BRCA2 or ATM gene would not be immediately distinguishable from an individual with a mutation in the other gene. This was particularly true when the BRCA2 mutation carrier phenotype was still largely undefined. It was therefore relevant to the ATM study that we further define the patient population with BRCA2 mutations and remove such individuals from our ATM study to the extent possible.

The BRCA2 gene was screened for mutations in probands from multiple high-risk breast cancer families. Several mutations in BRCA2 were identified in different families, and the penetrance and expressivity of BRCA2 mutations were calculated based on analysis of extended pedigrees (Schubert et al 1997a). BRCA2 mutation carriers were calculated to have a lifetime risk of breast cancer of 80%. This is a similar lifetime risk of breast cancer as BRCA1 mutation carriers, although BRCA2 mutation carriers average a slightly later age at diagnosis than BRCA1 mutation carriers. One family with a unique BRCA2 mutation (6425 del TT) in our series of high-risk breast cancer families is of Ashkenazi Jewish ancestry. The population genetics of BRCA1 and BRCA2 alleles in the Ashkenazi Jewish population is particularly interesting, as a particular BRCA1 as well as a particular BRCA2 mutation have both been shown to be prevalent in this population through ancient founder effects (reviewed in Szabo and King 1997). In order to better define the proportion of high-risk Ashkenazi Jewish breast cancer families with mutations in BRCA1 and BRCA2 and the fraction of the families accounted for by each mutation, we screened high-risk Ashkenazi Jewish breast cancer families for previously known and novel mutations in BRCA1 and BRCA2 (Schubert et al 1997b). This study indicated that approximately half of high-risk Ashkenazi Jewish breast cancer families could be accounted for by identified mutations in either BRCA1 or BRCA2, with the majority of families with identified mutations inheriting the previously identified ancient founder mutations. Mutations in other gene(s) are likely to be accountable for the inherited predisposition seen in the other half of the families in this series.

Table 1: Mutations in ATM in Selected Exons
(The Ataxia-Telangiectasia Mutation Database, unless otherwise noted)

Exon	Mutation	Consequence	Number of Times Reported Worldwide[1]
12	1240C>T	premature stop codon	2
12	1339C>T	premature stop codon	1
12	1563delAG	frameshift and truncation	3
15	2113delT	frameshift and truncation	1
15	2114ins/del6	codon change	>2[2]
17	2251del19	splicing deletion and truncation	1
17	2251del217	splicing deletion and truncation	2
17	2284delCT	frameshift and truncation	2
23	3078del207	splicing deletion and truncation	1
23	3109del73	frameshift and truncation	1
38	5319ins9	in-frame addition	>1
38	5320del7	frameshift and truncation	1
38	5320del355	splicing deletion and truncation	1
40	5675del88	splicing deletion and truncation	1
40	5712insA	frameshift and truncation	1
43	6007del89	splicing deletion and truncation	2
43	6015insC	frameshift and truncation	1
43	6056delA	frameshift and truncation	1
44	6096del103	splicing deletion and truncation	1
44	6100C>T	premature stop codon	2
46	6348del105	splicing deletion and truncation	1
46	6372insG	frameshift and truncation	1
46	6404insTT	frameshift and truncation	2
51	7271T>G	codon change (valine to glycine)	2[3]
51	7278del6	in-frame deletion	1
53	7517del4	frameshift and truncation	7
54	7630del159	splicing deletion and truncation	6[3]
54	7636del9	in-frame deletion	9[2,4]
54	7668del4	frameshift and truncation	1
55	IVS 54 -3 T>G	splicing deletion and truncation	1
55	7792C>T	premature stop codon	1
55	7883del5	frameshift and truncation	2
55	7926A>C	splicing deletion and truncation	1
58	8266A>T	premature stop codon	3
59	IVS 59+1 del4	splicing deletion and truncation	2
59	8269del150	splicing deletion and truncation	1
59	8269del403	splicing deletion and truncation	1
59	8269del2	frameshift and truncation	1
59	8283dTC	frameshift and truncation	1
59	8307G>A	premature stop codon	1
60	8473C>T	premature stop codon	1[4]
60	8480T>G	codon change; reduced protein levels	1
60	8535G>A	premature stop codon	1[4]
60	8578del3	in-frame deletion	1
64	8946insA	frameshift and truncation	1
64	8977C>T	premature stop codon	1
64	8985del13	frameshift and truncation	1

[1] Minimum number of times observed, as not all observations have been reported in the literature.
[2] This variant has been seen in Swedish breast cancer patients (Vorechovsky et al 1996)
[3] This variant has been seen in British AT families with breast cancer (Taylor et al 1997)
[4] This variant has also been reported in US breast cancer patients (FitzGerald et al 1997)

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